

### REMARKS

Applicants thank the Examiner for the phone conference of February 27, 2003. Applicants note that in the Office Action Summary, and on page 2 of the Office Action, the Examiner indicated that claim 21 was withdrawn from consideration. The Examiner also indicated, however, that claim 21 stands rejected (in the Office Action Summary, and on page 4 of the Office Action). In the Restriction Requirement of August 27, 2002, claim 21 was assigned to Group I, which is the Group that Applicants elected in their Response to Restriction Requirement of September 25, 2002. Therefore, Applicants believe that claim 21 is pending, and respectfully request confirmation from the Examiner.

Applicants respectfully requests entry of the amendments and remarks submitted herein. Claims 1, 5, 7-10, 12, and 22-23 have been amended. Claims 1-15, and 21-27 are currently pending. Attached is a marked-up version of the changes being made by the current amendments. Reconsideration of the pending application is respectfully requested.

#### The 35 U.S.C. §112 Rejections

Claims 1-15 and 22-27 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed.

The Examiner stated that claims 1, 10, and 12 are indefinite for omitting a method step to determine or extract the T wave morphology from the signals that are representative of electrical activity of the heart. Applicants have amended claims 1, 10, and 12 to recite that the first step of the method is to "obtain T wave signals representative of electrical activity of the heart..." Applicants submit that the steps of the claimed methods are complete and there are no steps that are omitted.

The Examiner indicated that claims 5, 7, 8, and 9 are indefinite for not positively reciting the method step. Applicants have amended claims 5, 7, 8, and 9 so that the method steps are positively recited.

The Examiner stated that certain limitations in claim 22 are inferentially included and are not positively recited. Applicants submit that the "programmable processor" recited in claim 22 is not being claimed. In addition, Applicants have amended claim 22 to specify that the fluctuations in T wave morphology are identified in T wave signals.

The Examiner indicated that claims 5, 9, and 23 are indefinite for reciting phrases that lack antecedent basis. Applicants have amended claims 5, 9, and 23.

Accordingly, Applicants respectfully request that the rejection of claims 1-15 and 22-27 under 35 U.S.C. §112, second paragraph, be withdrawn.

#### The 35 U.S.C. §102 Rejections

Claims 1, 7-10, 12, 14, 15, 21, and 22 stand rejected under 35 U.S.C. §102(b) as being anticipated by Kunig (U.S. Patent No. 4,622,980) or under 35 U.S.C. §102(e) as being anticipated by Ekwall (U.S. Patent No. 6,016,443). Applicants respectfully traverse these rejections.

The Examiner indicated that the rejected claims are "clearly anticipated" by the Kunig reference or by the Ekwall reference, but provides no explanation of how or why the Kunig reference or the Ekwall reference anticipates the pending claims.

The Kunig reference is directed toward a stress index and methods of determining such an index using a particular repolarization measurement. The Kunig reference discloses that a stress index is determined by calculating the ratio of the peak R wave to the peak T wave before and after stress. The Kunig reference makes no mention of non-alternating beat-to-beat fluctuations in T wave signals, or to T wave lability, as the pending claims recite. The Kunig reference, therefore, clearly does not anticipate the claimed invention.

The Ekwall reference is directed toward an ischemia detector that determines if the QT interval (*i.e.*, the interval between the Q wave and the T wave) gets shorter under certain workloads. A shortening of the QT interval indicates an ischemic condition. The Ekwall reference also discloses that an increase in the T wave amplitude also can indicate an ischemic condition. Applicants' specification defines T wave lability as the non-alternating beat-to-beat fluctuations in T wave signals (see, for example, page 5, lines 25-26). Applicants' specification also discloses that T wave lability can be measured (*i.e.*, as a T wave lability index), in part, by

calculating differences at every isochronic point along the repolarization interval between consecutive pairs of T waves (see, for example, page 8, lines 3-9 for a detailed description of calculating a T wave lability index). The Ekwall reference does not teach or suggest the existence of non-alternating beat-to-beat fluctuations in T wave morphology. Therefore, the Ekwall reference certainly does not measure changes in T wave amplitude on a beat-to-beat basis, and similarly, does not measure or determine a T wave lability value that reflects this non-alternating beat-to-beat variability in T waves. As such, the Ekwall reference clearly does not anticipate the pending claims.

Neither the Kunig reference nor the Ekwall reference teaches non-alternating beat-to-beat fluctuations in T wave morphology, and therefore, cannot anticipate the claimed invention. In view of the remarks herein, Applicants respectfully request that the rejection of claims 1, 7-10, 12, 14, 15, 21, and 22 under 35 U.S.C. §102(a) and §102(e) be withdrawn.

#### The 35 U.S.C. §103 Rejections

Claims 2-6, 11, and 13 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Ekwall or Kunig in view of Ben-Haim (U.S. Patent No. 6,285,898). This rejection is respectfully traversed.

The Examiner indicated that the Ekwall and Kunig references disclose all of the claimed limitations but do not speak explicitly to chemically stressing the patient. The Examiner stated, however, that the Ben-Haim reference teaches a method of detecting cardiovascular disease that includes a chemical stressing step for patients in whom an exercise stress test is not possible. The Examiner asserted that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method and apparatus of determining stress in a subject as disclosed in the Ekwall or Kunig reference with chemically stressing the patient as disclosed in the Ben-Haim reference.

Neither the Kunig reference nor the Ekwall reference teach or suggest the claimed methods. As discussed above, neither reference teaches or suggests a non-alternating beat-to-beat fluctuation in T wave morphology. Moreover, neither reference teaches or suggests that such non-alternating beat-to-beat variability could be quantitated to determine a value (*i.e.*, T

wave lability). In addition, neither reference teaches or suggests that such a value could be used to evaluate a person's risk for sudden death due to cardiovascular pathology.

The Ben-Haim reference is directed toward measuring electrical and non-electrical features of a cardiac muscle. The Ben-Haim reference discloses that electrical features can be obtained using an ECG, while non-electrical features can be obtained using an ultrasound device (*e.g.*, to measure perfusion) or an ionic sensor (*e.g.*, to measure changes in ion concentration), for example. With respect to the pending claims, the Ben-Haim reference does not cure the deficiencies of the Kunig and Ekwall reference. Therefore, the combination of the Kunig reference with the Ben-Haim reference, or the combination of the Ekwall reference with the Ben Haim reference, does not render obvious the pending claims. Accordingly, Applicants respectfully request that the rejection of claims 2-6, 11, and 13 under 35 U.S.C. §103 be withdrawn.

Claims 23-27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Ekwall or Kunig. This rejection is respectfully traversed.

The Examiner stated that the Ekwall or the Kunig reference discloses all of the claimed limitations but do not explicitly speak to eliminating ectopic beats, calculating the maximal value rms differences, filtering the electrical signal, removing baseline fluctuation, and normalizing the rms differences to signal-averaged QRS complexes. The Examiner asserted that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method and apparatus for determining a stress conditions of a patient to include eliminating ectopic beats, calculating the maximal value rms differences, filtering the electrical signal, removing baseline fluctuation, and normalizing the rms differences to signal-averaged QRS complexes, since it was well known in the art to use such signal processing techniques to remove noise and increase the signal to noise ratio in the electrical signals.

Since the T wave lability described herein would appear as broadband noise in the power spectrum of most ECGs (for example, a T wave alternans (TWA) analysis), it would not have been obvious to one of ordinary skill in the art at the time of the invention that non-alternating beat-to-beat fluctuations in T wave morphology even existed. Therefore, it would not have been

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obvious as to how to manipulate the signal processing to measure and quantitate such non-alternating beat-to-beat fluctuations.

Alone or in combination, the cited references do not teach or suggest the claimed computer-readable storage medium. In view of the above remarks, Applicants respectfully request that the rejection of claims 23-27 under 35 U.S.C. §103 be withdrawn.

#### CONCLUSION

Applicants ask that claims 1-15 and 21-27 be allowed. Enclosed is the \$55 fee for the Petition for One-Month Extension of Time. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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M. Angela Parsons  
M. Angela Parsons, Ph.D.  
Reg. No. 44,282

Fish & Richardson P.C., P.A.  
60 South Sixth Street, Suite 3300  
Minneapolis, MN 55402  
Telephone: (612) 335-5070  
Facsimile: (612) 288-9696

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1, 5, 7-10, 12, and 22-23 have been amended as follows:

1. (Amended) A method of detecting T wave lability in an individual, the method comprising:

obtaining T wave signals representative of electrical activity of the heart of said individual; and

detecting non-alternating beat-to-beat fluctuations in T wave morphology in said signals,

wherein said non-alternating beat-to-beat fluctuations in said T wave morphology is indicative of an individual having T wave lability.

5. (Amended) The method of claim [1] 2, wherein [the amount of] said chemical stressor is administered in an amount suitable [selected] to achieve a heart rate within a desired range.

7. (Amended) The method of claim 1, wherein said[ electrical signal is obtained] obtaining step is from a precordial lead V4.

8. (Amended) The method of claim 1, [wherein] further comprising generating said electrical signals [are generated ]into an electrocardiogram.

9. (Amended) The method of claim 1, [wherein the] further comprising monitoring a heart rate of said individual[ is monitored].

10. (Amended) A method for detecting or monitoring abnormal cardiac activities in an individual, the method comprising:

obtaining T wave signals representative of electrical activity of the heart of said individual; and

detecting the presence of non-alternating beat-to-beat fluctuations in T wave morphology in said signals,

wherein the presence of non-alternating beat-to-beat fluctuations in T wave morphology is indicative of abnormal cardiac activities in said individual.

12. (Amended) A method of assessing the risk of an individual for sudden death due to cardiovascular pathology, the method comprising:

obtaining T wave signals representative of electrical activity of the heart of said individual;

detecting the presence of non-alternating beat-to-beat fluctuations in T wave morphology in said signals; and

determining a T wave lability index from said non-alternating beat-to-beat fluctuations in T wave morphology,

wherein a T wave lability index that is significantly different than a reference value is indicative of an increased risk of said individual for sudden death due to a cardiovascular disease.

22. (Amended) A computer-readable storage medium having instructions stored thereon for causing a programmable processor to:

identify non-alternating beat-to-beat fluctuations in T wave morphology in T wave signals representative of electrical activity of the heart of an individual; and

determine a T wave lability index as a function of said non-alternating beat-to-beat fluctuations in T wave morphology.

23. (Amended) The computer-readable storage medium of claim 22, wherein said determining a T wave lability index as a function of said non-alternating beat-to-beat fluctuations in T wave morphology comprises eliminating ectopic beats and [the] sinus beats preceding and following said ectopic beats and calculating the maximal value of root-mean-square differences for isochronic points of [the] a repolarization interval between pairs of consecutive beats.